AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph beginning on page 12, line 23 and ending on page 13, line 6 with the following amended paragraph.

The sample solution can be any solution containing an analyte or analytes of interest. Because sample passes through an open channel, the extraction capillaries of the invention are relatively tolerant of particulate matter in the sample solution compared to packed bed extraction columns. Still, it is often useful to clarify a crude sample prior to introduction into the channel, e.g., by centrifugation or filtration. Examples of sample solutions would include cell lysastes, serum-free hybridoma growth medium, tissue or organ extracts, biological fluids, cell-free translation or transcription reactions, or organic synthesis reaction mixtures. In some cases the sample solution is the analyte in a solvent used to dissolve or extract the analyte from a biological or chemical sample. The solvent should be sufficiently weak to ensure sufficient adsorption of the analyte to the channel's extraction surface. Ideally, the adsorption is quantitative, near quantitative, or at least involves a substantial amount of the analyte. Nevertheless, the process can still be very useful where only some smaller fraction of the total analyte is adsorbed, depending upon the nature of the analyte, the amount of starting material, and the purpose for which the analyte is being processed.

Please replace the paragraph beginning on page 33, line 13 and ending on page 34, line 2 with the following amended paragraph..

In some embodiments of the invention, the affinity binding reagent is one that recognizes one or more of the many affinity groups used as affinity tags in recombinant fusion proteins. Examples of such tags include poly-histidine tags (e.g., the 6X-His tag), which can be extracted using a chelated metal such as Ni-NTA- peptide sequences (such as the FLAG epitope) that are recognized by an immobilized antibody; biotin, which can be extracted using immobilized avidin or streptavidin; "calmodulin binding peptide" (or, CBP), recognized by calmodulin charged with calcium- glutathione S-transferase protein (GST), recognized by immobilized glutathione; maltose binding protein (MBP), recognized by amylose; the cellulose-binding domain tag, recognized by immobilized cellulose; a peptide with specific affinity for S-protein (derived from ribonuclease A); and the peptide sequence tag CCxxCC (where xx is any amino acid, such as RE), which binds to the affinity binding agent bis-arsenical fluorescein (FIAsH dye).

Please replace the paragraph on pages 37, lines 15 – 27 with the following amended paragraph.

In some embodiments, the invention is used to prepare an ~~analtye~~analyte for use in an analytical method that involves the detection of a binding event on the surface of a solid substrate. These solid substrates are generally referred to herein as "binding detection chips," examples of which include hybridization microarrays and various protein chips. As used herein, the term "protein chip" is defined as a small plate or surface upon which an array of separated, discrete protein samples (or "dots") are to be deposited or have been deposited. In general, a chip bearing an array of discrete ligands (e.g., proteins) is designed to be contacted with a sample having one or more biomolecules which may or may not have the capability of binding to the surface of one or more of the dots, and the occurrence or absence of such binding on each dot is subsequently determined. A reference that describes the general types and functions of protein chips is Gavin MacBeath, Nature Genetics Supplement, 32:526 (2002). See also Ann. Rev. Biochem., 2003 72:783-812.

Please replace the paragraph on pages 39, lines 13 – 29 with the following amended paragraph.

In this and related embodiments, a protein is purified and/or concentrated using an extraction channel method as described herein, and then spotted at a predetermined location on the chip. In preferred embodiments, the protein is spotted directly from an extraction capillary onto the substrate. That is, the protein is extracted from a sample solution and then eluted in a desorption solution directly onto the chip. Of course, in this embodiment it is important that the desorption solution be compatible with the substrate and with any chemistry used to immobilize or affix the protein to the substrate. Typically, a ~~microarry~~microarray format involves multiple spots of protein samples (the protein samples can all be the same or they can be different from one another). Multiple protein samples can be spotted sequentially or simultaneously. Simultaneous spotting can be achieved by employing a multiplex format, where an array of extraction capillaries is used to purify and spot multiple protein samples in parallel. The small size and portability made possible by the use of capillaries facilitates the direct spotting of freshly purified samples, and also permits multiplexing formats that would not be possible with bulkier conventional protein extraction devices. Particularly

when very small volumes are to be spotted, it is desirable to use a pump capable of the accurate and reproducible dispensing of small volumes of liquid, as described elsewhere herein.

Please replace the paragraph on pages 52, lines 1 – 26 with the following amended paragraph.

The possible means for fluid manipulation are varied. For example, another embodiment of the invention particularly suited for use in a multiplex context is illustrated in Figures 7A-J. The embodiment employs a manifold 52, which includes a plunger-barrel 54, a precision plunger 56 slidably positioned in the manifold so that it can slide through barrel 58, and an inlet port 60 in communication with the barrel 58 (Fig. 7A). In operation, a disposable cartridge 70, comprising a fluid reservoir 72 and a capillary holder 74 is attached to the manifold by sliding the end of the plunger-barrel into the reservoir (Fig. 7B). A seal between the plunger-barrel and the wall of the reservoir is achieved by means of the seal 76. The lower end of the capillary 78 is brought into contact with sample solution 80, contained in sample vial 82, which is positioned in a sample tray. Sample solution is drawn from the sample vial through the capillary and into the reservoir through the upper end of the capillary 84. The sample solution is drawn into and out of the disposable reservoir by lowering the precision plunger 56 to seal the top 50 of the plunger-barrel 54 and pushing and pulling the barrel-plunger 54 like a syringe (Figs. 7C-7D). The precision plunger 56 is then raised and wash solution is blown through the port 60, the reservoir 72 and out through the capillary 74 (Fig. 7E). The plunger-barrel 54 is then lowered to the bottom of the reservoir (Fig. 7F). Optionally, a second wash (e.g., water) can be blown through the port 60 and through the capillary in down position. Nitrogen is then blown through the port 60 and into the capillary 74 to purge the capillary (Fig. 7G). The lower end of the capillary 78 is inserted into desorption solution 92 (Fig. 7H). The precision plunger 56 is then operated to draw a slug of desorption solution through the capillary until it reaches near the end 84 without entering the barrel (Fig. 7J). The precision plunger 56 is used to control the movement of the plug back and forth in the capillary as described elsewhere herein, and finally the slug of ~~deorption~~desorption solution containing eluted analyte is collected in a sample vial 94 or deposited on a target (Fig. 7J).

Please replace the paragraph on pages 55, lines 3 – 7 with the following amended paragraph.

In some embodiments, one or more dimensions of a multidimensional extraction are achieved by means other than an extraction capillary. For example, the first dimension separation might be accomplished using conventional chromatography, ~~electophoresis~~electrophoresis, or the like, and the fractions then loaded on an extraction capillary for separation in another dimension.

Please replace the paragraph beginning on page 59, line 30 and ending on page 60, line 9 with the following amended paragraph.

One particular aspect of the extraction capillary technology of the invention that facilitates non-denaturing extraction is that the process can be accomplished at low temperatures. In particular, because solution flow through the capillary can be done without heating the capillary, e.g., without the introduction of electrical current or the generation of joule heat that typically accompanies capillary processes involving chromatography or electroosmotic flow, the process can be carried out at lower temperatures. Lower temperature could be room temperature, or even lower, e.g., if the process is carried out in a cold room, or ~~the~~ a cooling apparatus is used to cool the capillary. For example, capillary extractions can be performed at a temperature as low as ~~0~~0°C, 2°C or 4°C, e.g., in a range such as ~~0~~0°C to 30°C, ~~0~~0°C to 20°C, 2°C to 30°C, 2°C to 20°C, 4°C to 30°C, or 4°C to 20°C.

Please replace the paragraph on pages 60, lines 19 – 24 with the following amended paragraph.

In another aspect, extracted protein is sometimes stabilized by maintaining it in a hydrated form during the extraction process. For example, if a purge step is used to remove bulk liquid (i.e., liquid segments) from the capillary prior to ~~desporption~~desorption, care is taken to ensure that gas is not blown through the capillary for an excessive amount of time, thus avoiding drying out the capillary and possibly desolvating the extraction phase and/or protein.

Please replace the two paragraphs on page 61 lines 7 – 19 with the following two amended paragraphs.

The recovery of non-~~denatured~~denatured, native, functional and/or active protein is particularly useful as a preparative step for use in processes that require the protein to be denatured

in order for the process to be successful. Non-limiting examples of such processes include analytical methods such as binding studies, activity assays, enzyme assays, X-ray crystallography and NMR.

In another embodiment, the invention is used to stabilize RNA. This can be accomplished by separating the RNA from some or substantially all ~~RNAse~~RNase activity, enzymatic or otherwise, that might be present in a sample solution. In one example, the RNA itself is extracted and thereby separated from ~~RNAse~~RNase in the sample. In another example, the RNase activity is extracted from a solution, with stabilized RNA flowing through the capillary. Extraction of RNA can be sequence specific or non-sequence specific. Extraction of ~~RNAse~~RNase activity can be specific for a particular ~~RNAse~~RNase or class of ~~RNAses~~RNases, or can be general, e.g., extraction of proteins or subset of proteins.

Please replace the paragraph on pages 65, lines 21 – 27 with the following amended paragraph.

Specific cells, classes of cells, viruses and the like can be extracted by using an extraction phase with an affinity for a moiety characteristic to the analyte of interest, e.g., a protein or other biomolecule displayed on the surface of the cell or virus. Many cell types (e.g., cancer cells, types of B cells and T cells, etc.) display characteristic antigenic groups that can be recognized by the corresponding antibody. This antibody can be immobilized to the interior of the extraction channel and ~~finiction~~function as an affinity group specific for the cell or virus type of interest.

Please replace the paragraph on pages 77, lines 8 – 11 with the following amended paragraph.

The objective of this assay is to determine the amount of Ni^{2+} ions bound to capillary surface by chelation to the NTA moieties. Ni^{2+} ions (in aqueous solution) form a stable, colored complex (2:1) with 4-(2-pyridylazo) resorcinol ("PAR"), with ~~=~~A_{max} = 495nm.

Please replace the paragraph on pages 77, lines 21 – 22 with the following amended paragraph.

The relationship between Ni^{2+} capacity and protein capacity was determined for several different capillaries (see Table), using the procedures of Examples 13 and 18.